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10/802,000	03/16/2004	Thomas Nadackal Thomas	1996.01	2824

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EXAMINER	
JAGOE, DONNA A	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/802,000	THOMAS, THOMAS NADACKAL	
	Examiner	Art Unit	
	Donna Jagoe	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *6,8-16,18,19 and 21-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,17 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 26, 2008 has been entered.

Claims 1-34 are pending in this application. Claims 6, 8-16, 18, 19 and 21-34 are withdrawn from consideration. Claims 1-5, 7, 17 and 20 are rejected.

Applicants' arguments filed November 26, 2008 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7, 17 and 20 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,

5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to a method of "preventing, reducing and reversing the toxic side-effects" caused by anti-inflammatory drugs with a MAO inhibitor.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might

behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain).

The Merck Manual (http://www.merck.com/mmpe/sec02/ch013/ch013a.html), cited for evidentiary purposes, teaches that NSAIDs promote mucosal inflammation and ulcer formation (sometimes with GI bleeding) both topically and systemically. By inhibiting prostaglandin production via blockage of the enzyme cyclooxygenase (COX), NSAIDs reduce gastric blood flow, reduce mucus and HCO_3 secretion, and decrease cell repair and replication. Also, because NSAIDs are weak acids and are nonionized at gastric pH, they diffuse freely across the mucus barrier into gastric epithelial cells, where H^+ ions are liberated, leading to cellular damage. Because gastric prostaglandin production involves the COX-1 isoform, NSAIDs that are selective COX-2 inhibitors have fewer adverse gastric effects than other NSAIDs.

This article plainly demonstrates that there is a wide spectrum of gastrointestinal toxicities associated with nonsteroidal anti-inflammatory drugs.

2. The breadth of the claims

The claims are extremely broad insofar as they disclose the prevention of toxic gastrointestinal effects comprising administering a MAO inhibitor.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to reduce all of the various side effects of anti-inflammatory drugs. Aside from a teaching of protection from gastric lesion (ulceration) with L-deprenyl or propargylamine when aspirin or indomethacin was administered for 7 days, in a rat, there is no evidence that the claimed combination has any effect in preventing long term side effects. Applicant's results only demonstrate that the l-deprenyl prevented aspirin or indomethacin induced ulcer formation in a rat for 7 days.

4. The quantity of experimentation necessary

Because of the known **unpredictability** of the art and the broad spectrum of toxicities associated with anti-inflammatory agents (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed combination could be predictably used to lower the side effects caused by antineoplastic agents as inferred in the claims and contemplated by the specification.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicants have presented a general idea that because aspirin or indomethacin administered with l-deprenyl is not acutely toxic to mice then this combination must, *a priori*, be useful to "prevent toxic gastrointestinal side effects caused by anti-inflammatory agents with a MAO inhibitor. As such, it is entirely speculative that administration of aspirin or indomethacin combined with l-deprenyl.

Determining if any particular toxic gastrointestinal side effect of any particular MAO inhibitor would be prevented simply by administration of l-deprenyl or propargylamine would require extensive testing in human subjects, with no direction or guidance provided by Applicants for such testing. This is undue experimentation given the limited guidance and direction provided by Applicants. As noted *supra*, even *in vitro* and *in vivo* assays do not always correlate to efficacy in humans and are not generally predictive of clinical efficacy.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 5 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: applicant claims the anti-inflammatory drugs are selected from "statins". There is no definition in the instant specification as to what is included or excluded by the term "statins". Does this term include nystatin, somatostatin, cilastatin? These are not HMG-CoA reductase inhibitors, but they are words then end with "statin".

Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The term "acetaminophen" in claim 2 is used by the claim to mean "an anti-inflammatory drug", while it is well known that acetaminophen has analgesic and antipyretic properties, but it does not have anti-inflammatory properties. The term is indefinite because the specification does not clearly redefine the term.

Regarding claim that 1 recites the term (MAO inhibitor) in line 5 of the claim, it is customary that the full name of the abbreviation be recited the first time the abbreviation is used in the claims. The meaning of every term used in a claim should be apparent from the prior art or from the specification and drawings at the time the application is filed. Applicants need not confine themselves to the terminology used in the prior art,

but are required to make clear and precise the terms that are used to define the invention whereby the metes and bounds of the claimed invention can be ascertained. During patent examination, the pending claims must be given the broadest reasonable interpretation consistent with the specification. In re Morris, 127 F.3d 1048, 1054, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997); In re Prater, 415 F.2d 1393, 162 USPQ 541 (CCPA 1969).

Similarly, claim 2 recites the abbreviations NSAIDs and COX-3 inhibitors. Claim 3 recites COX-1 inhibitor and COX-2 inhibitor without reciting the full name of the abbreviation first.

Claim 7 recites the limitation "a method according to claim 1, wherein the MAO inhibitor treats, prevents decreases or reverses the toxic side effects of anti-inflammatory drugs consisting of renal damage, liver damage and platelet dysfunction" There is insufficient antecedent basis for this limitation in the claim because the toxic side effects according to claim 1 are limited to the gastrointestinal side effects.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-5, 7, 17 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glavin et al. (cite No. 4 IDS dates 3/16/04) and Lianping et al (U).

Glavin et al. teach there is an association between the occurrence of duodenal ulcers and dopamine deficiency in disorders such as Parkinson's disease. In addition, disorders characterized by excess dopamine activity, such as schizophrenia are rarely associated with duodenal pathology. It was shown that pretreatment with a selective MAO_b inhibitor, L-deprenyl, prevented duodenal ulcers in rats when they were administered the agent 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). (see page 379)

It does not teach a method of preventing, reducing, and reversing the toxic effects of anti-inflammatory drugs comprising administration of an MAO inhibitor.

Lianping et al. teach MAO inhibitors reduced restraint stress-induced gastric ulceration by inhibition of gastrin release (page 61) resulting in a protection of the gastric mucosa (page 63, column 1).

It does not teach a method of preventing, reducing, and reversing the toxic effects of anti-inflammatory drugs comprising administration of an MAO inhibitor.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to employ MAO inhibitors to prevent the toxic effects of anti-inflammatory agents motivated by the teaching of Glavin et al. that L-deprenyl, prevented duodenal ulcers in rats when they were administered the agent 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a dopamine depleting agent, known to cause gastric mucosal injury, thus demonstrating the protective utility of MAO inhibitors and by the teachings of Lianping et al. who demonstrates further inhibition of stress induced gastric ulceration by administration of MAO inhibitors to rats whereby release of gastrin is inhibited.

The protective gastrointestinal effect is disclosed in both references. It would have been obvious to employ the MAO inhibitors to provide a protective effect to the gastrointestinal mucosa when NSAIDs are administered.

One of ordinary skill in the art would have been capable of applying this known technique to a known method that was ready for improvement and the results would have been predictable to one of ordinary skill in the art.

Thus the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Accordingly, for the above reasons, the claims are deemed properly rejected and none are allowed.

Response to Arguments

Applicant asserts that Glavin and Lianping studied only stress induced ulcers caused by cold exposure and Lianping expressly limited its teachings to determining protection via antisecretory effects of MAP-B inhibition. Applicant asserts that claim 1 is limited to NSAID induced gastric injury, however this does not appear to be the case. Claim 1 is limited to anti-inflammatory agents, that are selected from NSAIDs, steroids, acetaminophen, COX-3 inhibitors , 5-lipoxygenase inhibitors, leukotriene receptor antagonists, leukotriene A4 hydrolase inhibitors, angiotensin converting enzyme antagonists, antihistaminics, histamine 2 receptor antagonists, phosphodiesterase-4 antagonists, cytokine antagonists, CD44 antagonists, antineoplastic agents, 3-hydroxy-3-methylglutaryl coenzyme A inhibitors, statins, alpha blockers, beta blockers, estrogens, androgens, antiplatelet agents, antidepressants, Helicobacter pylori inhibitors, proton pump inhibitors, thiazolidinediones, dual-action compounds, combinations of these drugs with other agents, derivatives and metabolites of antiinflammatory agents. Further, the definition of anti-inflammatory toxicity is similarly broad in that it encompasses MAO inhibition, neuroprotection, endothelial protection, antiinflammatory action, antiplatelet action, antiatherogenic action, inhibition of activation and migration of leukocytes, decreasing the levels inflammatory markers, antioxidant action, free radical scavenging, antiapoptotic action, reduction of hypoxia, reduction of oxidative stress, antagonism of cytotoxic actions of toxic agents, inhibition of tumor growth, vasodilation, increased blood flow, enhanced expression of antioxidant enzymes and growth factors, stimulation of constitutive nitric oxide synthase enzymes

resulting in the enhanced production of nitric oxide, and inhibition of cytochrome P450 enzymes (instant claim 5). As such, all that is required of the MAO inhibitor is to inhibit monoamine oxidase to meet the claim.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Friday from 8:00 A.M. - 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Donna Jagoe /D. J./

Examiner
Art Unit 1614

January 4, 2009

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614